CLAIMS

What is claimed is:

1. A method of obtaining a cell population enriched for long-term repopulating human hematopoietic stem cells, said method comprising obtaining a population of cells from human hematopoietic tissue and isolating a population of KDR^+ cells therefrom, thereby obtaining a cell population enriched for long-term repopulating human hematopoietic stem cells.

2. The method of claim 1, wherein said human hematopoietic tissue is selected from the group consisting of pre-embryonic hematopoietic tissue, embryonic hematopoietic tissue, fetal hematopoietic tissue, and post-natal hematopoietic tissue.

3. The method of claim 2, wherein said embryonic hematopoietic tissue is selected from the group consisting of yolk sac, and embryonic liver.

4. The method of claim 2, wherein said fetal hematopoietic tissue is selected from the group consisting of fetal liver, fetal bone marrow and fetal peripheral blood.

5. The method of claim 2, wherein said post-natal hematopoietic tissue is selected from the group consisting of cord blood, bone marrow, normal peripheral blood, mobilized peripheral blood, hepatic hematopoietic tissue, and splenic hematopoietic tissue.

6. The method of claim 1, wherein said KDR^+ cells are isolated using a reagent which specifically binds KDR.

7. The method of claim 6, wherein said reagent is an antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

8. The method of claim 7, wherein said antibody is a monoclonal antibody.

9. The method of claim 8, wherein said monoclonal antibody is 260.4.

10. The method of claim 1, wherein said KDR^+ cells are isolated using a conjugated vascular epithelial growth factor or a molecule derived therefrom.

11. The method of claim 1, wherein said cells are starvation resistant long-term repopulating human hematopoietic stem cells.

12. An enriched population of long-term repopulating human hematopoietic stem cells obtained using the method of claim 1.

13. A cell obtained using the method of claim 1.

14. The cell of claim 13, wherein said cell comprises an isolated nucleic acid.

15. The cell of claim 14, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deamininase, a nucleic acid encoding β-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

16. The cell of claim 14, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

17. The cell of claim 16, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

18. A method of obtaining a purified population of long-term repopulating human hematopoietic stem cells, said method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of hematopoietic progenitor cells therefrom, and isolating a population of KDR^+ cells from said population of hematopoietic progenitor cells, thereby obtaining a purified population of long-term repopulating human hematopoietic stem cells.

19. The method of claim 18, wherein said human hematopoietic tissue is selected from the group consisting of pre-embryonic hematopoietic tissue, embryonic hematopoietic tissue, fetal hematopoietic tissue, and post-natal hematopoietic tissue.

20. The method of claim 19, wherein said embryonic hematopoietic tissue is selected from the group consisting of yolk sac, and embryonic liver.

21. The method of claim 19, wherein said fetal hematopoietic tissue is selected from the group consisting of fetal liver, fetal bone marrow and fetal peripheral blood.

22. The method of claim 19, wherein said post-natal hematopoietic tissue is selected from the group consisting of cord blood, bone marrow, normal peripheral blood, mobilized peripheral blood, hepatic hematopoietic tissue, and splenic hematopoietic tissue.

23. The method of claim 18, wherein said hematopoietic progenitor cells are isolated using at least one method selected from the group consisting of isolation of cells expressing an early marker using antibodies specific for said marker, isolation of cells not expressing a late marker using antibodies specific for said late marker, isolation of cells based on a physical property of said cells, and isolation of cells based on a biochemical/biological property of said cells.

24. The method of claim 23, wherein said early marker is selected from the group consisting of CD34, Thy-1, c-kit receptor, flt3 receptor, AC133, vascular endothelial growth factor receptor I, vascular endothelial growth factor receptor III, Tie1, Tek, and basic fibroblast growth factor receptor.

25. The method of claim 23, wherein said late marker is a lineage (lin) marker.

26. The method of claim 24, wherein said early marker is CD34.

27. The method of claim 26, wherein said hematopoietic progenitor cells are obtained from said hematopoietic tissue using an antibody which specifically binds CD34 to select a population of $CD34^+$ hematopoietic progenitor cells.

28. The method of claim 27, wherein said population of KDR^+ cells is isolated from said population of $CD34^+$ hematopoietic progenitor cells using an antibody which specifically binds KDR.

29. The method of claim 28, wherein said antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

30. The method of claim 29, wherein said antibody is a monoclonal antibody.

31. The method of claim 30, wherein said monoclonal antibody is 260.4.

32. The method of claim 31, wherein said cells are starvation resistant human hematopoietic stem cells.

33. An isolated purified population of long-term repopulating human hematopoietic stem cells obtained by the method of claim 17.

34. A cell obtained by the method of claim 17.

35. The cell of claim 34, wherein said cell comprises an isolated nucleic acid.

36. The cell of claim 35, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding β-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

37. The cell of claim 35, wherein said isolated nucleic acid is operably ~~linked to a promoter/regulatory sequence.~~

38. The cell of claim 37, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

39. The method of claim 26, wherein said hematopoietic progenitor cells are obtained from said hematopoietic tissue using antibody which specifically binds CD34 to select a population of $CD34^-$ cells.

40. The method of claim 39, wherein said hematopoietic progenitor cells are obtained from said population of $CD34^-$ cells using antibody which specifically binds lin to select a population of $CD34^-lin^-$ cells.

41. The method of claim 40, wherein said population of KDR^+ cells is isolated from said population of $CD34^-lin^-$ cells using an antibody which specifically binds KDR.

42. The method of claim 41, wherein said antibody is selected from the group consisting of a polyclonal antibody and a monoclonal antibody.

43. The method of claim 42, wherein said antibody is a monoclonal antibody.

44. The method of claim 43, wherein said monoclonal antibody is 260.4.

45. A purified population of long-term repopulating human hematopoietic stem cells obtained by the method of claim 41.

46. A cell isolated by the method of claim 41.

47. The cell of claim 46, wherein said cell comprises an isolated nucleic acid.

48. The cell of claim 47, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding β-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

49. The cell of claim 48, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

50. The cell of claim 49, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

51. A method of expanding a population of long-term repopulating human hematopoietic stem cells, the method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of KDR^+ hematopoietic stem cells therefrom, and incubating said population of KDR^+ cells with vascular endothelial growth factor, thereby expanding said population of long-term repopulating human hematopoietic stem cells.

52. The method of claim 51, further comprising incubating said population of KDR^+ cells with at least one growth factor.

53. The method of claim 52, wherein said growth factor is selected from the group consisting of flt3 receptor ligand, kit receptor ligand, thrombopoietin,

basic fibroblast growth factor, interleukin 6, interleukin 11, interleukin 3, granulomonocytic colony-stimulatory factor, granulocytic colony-stimulatory factor, monocytic colony-stimulatory factor, erythropoietin, angiopoietin, and hepatocyte growth factor.

54. An isolated purified population of long-term repopulating human hematopoietic stem cells obtained by the method of claim 51.

55. A cell obtained using the method of claim 51.

56. The cell of claim 55, wherein said cell comprises an isolated nucleic acid.

57. The cell of claim 56, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding β-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

58. The cell of claim 57, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

59. The cell of claim 58, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

60. A blood substitute comprising the progeny cells of an isolated purified population of long term repopulating human hematopoietic stem cells.

61. The blood substitute of claim 60, wherein said progeny cells are selected from the group consisting of red blood cells, neutrophilic granulocytes, eosinophilic granulocytes, basophilic granulocytes, monocytes, dendritic cells, platelets, B lymphocytes, T lymphocytes, natural killer cells, and differentiated precursors thereof, and undifferentiated progenitors thereof.

62. A chimeric non-human mammal comprising at least one of an isolated and purified long-term repopulating human hematopoietic stem cell.

63. The chimeric mammal of claim 62, wherein said cell is introduced into said mammal using a method selected from the group consisting of transplantation, and blastocyst injection.

64. The non-human mammal of claim 63, wherein said mammal is selected from the group consisting of a mouse, a rat, a dog, a donkey, a sheep, a pig, a horse, a cow, a non-human primate.

65. A method of inhibiting rejection of a transplanted organ, said method comprising ablating the bone marrow of a transplant recipient and administering to said recipient a multi-lineage engrafting dose of an isolated and purified long-term repopulating human hematopoietic stem cell obtained from the hematopoietic tissue of the donor of said organ, thereby inhibiting rejection of a transplanted organ.

66. A method of transplanting an autologous human hematopoietic stem cell in a human, said method comprising obtaining a population of cells from the hematopoietic tissue of a human and isolating a population of non-malignant hematopoietic stem cells therefrom, ablating the bone marrow of said human, and administering at least one said isolated non-malignant hematopoietic stem cell to said

human, thereby transplanting an autologous human hematopoietic stem cell in a human.

67. A method of isolating a KDR^+ cell, said method comprising selecting a cell expressing an antigen coexpressed with KDR, thereby isolating a KDR+ cell.

68. The method of claim 67, wherein said coexpressed antigen is selected from the group consisting of a vascular endothelial growth factor receptor I, and a vascular endothelial growth factor receptor III.

69. A method of isolating a KDR+ stem cell giving rise to at least one of a muscle cell, a hepatic oval cell, a bone cell, a cartilage cell, a fat cell, a tendon cell, and a marrow stroma cell said method comprising isolating a KDR+ stem cell from hematopoietic tissue, thereby isolating a KDR+ stem cell giving rise to at least one of a muscle cell, a hepatic oval cell, a bone cell, a cartilage cell, a fat cell, a tendon cell, and a marrow stroma cell.

70. A method of monitoring the presence of KDR+ stem cells in a human hematopoietic tissue in a human receiving therapy, said method comprising obtaining a sample of hematopoietic tissue from said human before, during and after said therapy, and measuring the number of KDR+ stem cells in said sample, thereby monitoring the presence of KDR+ stem cells in a human hematopoietic tissue obtained from a human receiving therapy.